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Papers

Is the international normalised ratio (INR) reliable? A trial of comparative measurements in hospital laboratory and primary care settings

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Abstract

***Aim*—To determine the reliability of international normalised ratio (INR) measurement in primary care by practice nurses using near patient testing (NPT), in comparison with results obtained within hospital laboratories by varied methods.**

***Methods*—As part of an MRC funded study into primary care oral anticoagulation management, INR measurements obtained in general practice were validated against values on the same samples obtained in hospital laboratories. A prospective comparative trial was undertaken between three hospital laboratories and nine general practices. All patients attending general practice based anticoagulant clinics had parallel INR estimations performed in general practice and in a hospital laboratory.**

***Results*—405 tests were performed. Comparison between results obtained in the practices and those in the reference hospital laboratory (gold standard), which used the same method of testing for INR, showed a correlation coefficient of 0.96. Correlation coefficients comparing the results with the various standard laboratory techniques ranged from 0.86 to 0.92. It was estimated that up to 53% of tests would have resulted in clinically significant differences (change in warfarin dose) depending upon the site and method of testing. The practice derived results showed a positive bias ranging from 0.28 to 1.55, depending upon the site and method of testing.**

***Conclusions*—No technical problems associated with INR testing within primary care were uncovered. Discrepant INR results are as problematic in hospital settings as they are in primary care. These data highlight the failings of the INR to standardise when different techniques and reagents are used, an issue which needs to be resolved. For primary care to become more involved in therapeutic oral anticoagulation monitoring, close links are needed between hospital laboratories and practices, particularly with regard to training and quality assurance.**

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Oral anticoagulant monitoring has traditionally been hospital based, in part because of the need for a laboratory blood test. The growing numbers of patients receiving warfarin as a result of the increasing indications for anticoagulation—especially for non-rheumatic atrial fibrillation—have led to pressure on primary care to undertake therapeutic monitoring.[1 2] If this shift of care is to occur, it is important that the international normalised ratio (INR) can be reliably measured within primary care settings.

There are two potential obstacles to ensuring reliability: the provision of adequately trained personnel and the availability of suitable technology. The traditional belief has been that trained laboratory staff are needed to perform the test because of the complex operator dependent steps and the requirements of quality assurance.[3]

Concerns are expressed that laboratory testing within general practice settings is done poorly, and this issue would be particularly important for a test which results in treatment change.[4] Several portable instruments are available for INR estimation outside laboratory settings. These show good reliability in comparison with traditional laboratory techniques[5 6]; however, evaluations have only been performed in hospital settings using highly trained staff, with few data from primary care.[7]

The aim of anticoagulant treatment is to prevent thrombotic problems, while minimising the risks of bleeding caused by depression of clotting factors.[8] Recognition of the haemorrhagic side effects of warfarin led to the development of the prothrombin time test for monitoring anticoagulant activity.[9] The prothrombin time assesses the integrity of the extrinsic coagulation pathway including three of the clotting factors dependent upon vitamin K (factors II, VII, and X). The prothrombin

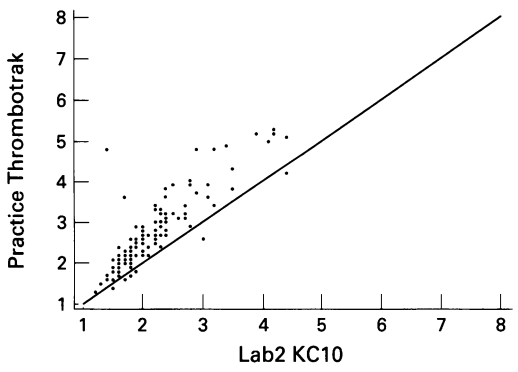

Figure 1 Practice Thrombotrak v Lab 2 KC10. Solid line represents line of identity.

time may vary, however, according to the specific thromboplastin used, with less sensitive thromboplastins giving a shorter prothrombin time.[10] The INR system, established as an attempt to standardise these discrepancies, is based on a quantitative assessment of the responsiveness of a thromboplastin by comparison with reference thromboplastins from the World Health Organisation (WHO).[11 12] This relative responsiveness is called the international sensitivity index (ISI). The INR is then calculated as INR = [prothrombin ratio]^{ISI}, where the prothrombin ratio is calculated by testing normal plasma against warfarin treated patient plasma in parallel with the local reagent and reference thromboplastin. The ISI is calculated from the orthogonal regression line of the calibration of the test reagent with a WHO international reference material.[13]

In this paper we investigate the reliability of INRs performed in primary care in comparison with parallel results obtained in hospital laboratories using the same samples.

Methods

As part of an MRC funded health technology assessment to investigate the possibility of transferring oral anticoagulant monitoring from secondary to primary care, a network of nine general practices was developed to manage warfarin patients using computerised decision support (CDSS) and near patient testing (NPT) for INR. This study was undertaken from 1 February 1995 until 31 January 1996. Thrombotrak (Nycomed UK) was used as the NPT, being the only instrument at the time that had undergone a positive UK Department of Health evaluation. The thromboplastin reagent used was Thrombotest (Nycomed UK), a WHO secondary reference thromboplastin with manufacturer's derived ISI of 1.0. The same batch of Thrombotest was used throughout the study.

To perform the INR test a venous sample of blood was collected in a citrated tube; 50 µl of this sample were added to 250 µl of reconstituted reagent, warmed to 37°C. Internal quality assurance (IQA) was performed before starting each practice clinic, with external quality assurance (EQA) performed every eight to 12 weeks. Both IQA and EQA were provided through the local reference laboratory (laboratory 1).

The remaining portions of the venous samples were sent to three local laboratories, which used four different methods to compare the INR results obtained. Blood samples were delivered to the hospitals by routine collection. In laboratory 1 the INR was estimated on two machines: Thrombotrak using Thrombotest from the same batch as that used by the practices (method 1a); and by ACL machine (Instrumentation Laboratory, UK, Ltd) using IL (PT-Fibrinogen HS plus) reagent (method 1b). The ISI of the ACL/IL combination was derived by the laboratory using an orthogonal regression calibration procedure, comparing manual and machine values obtained from 20 normal and 80 warfarinised patient plasmas, resulting in a value of 1.15. As laboratory 1 is recognised by the health authority as a regional reference laboratory, the INR derived using the ACL/IL combination is taken as the gold standard (method 1b).

In laboratory 2, INR was estimated by KC-10 machine using Manchester reagent, ISI 1.04 (method 2). In laboratory 3, INR was performed manually using Manchester reagent, ISI 1.03 (method 3). These ISIs were provided by the manufacturer, with no local calibration undertaken. All three laboratories participated in two external quality assurance schemes—NEQAS (national external quality assessment scheme) and CEQAS (central external quality assurance scheme). Five practices sent samples to laboratory 1, four practices sent samples to laboratory 2, with one of these practices changing to laboratory 3 during the study.

All practice based clinics were run by nurses, except for one which employed a medical laboratory scientific officer (MLSO) for the study. All practice based staff attended a one day training course which dealt with the theoretical aspects of oral anticoagulation as well as practical training in the use of CDSS and NPT. On site support was available for the first three clinics, although this was primarily needed for CDSS interpretation and clinical advice rather than help in performing the INR.

STATISTICS

Statistical methods used included linear regression analysis, paired *t* tests, and Wilcoxon signed rank tests on INR levels. Out of range frequencies were compared using χ^2 and McNemar tests. Not all analyses are reported here.

Results

Four hundred and five results were obtained from 296 patients receiving warfarin treatment: 196 were sent to laboratory 1, 141 to laboratory 2, and 68 to laboratory 3. The majority of samples were processed within six hours of venepuncture. No relation was found between time of INR testing and INR correlation.

For results obtained by the practices, 217 (54%) were within the individual therapeutic range. In comparison, in-range figures for the contemporaneous samples sent to the hospitals

Table 1 Laboratory 1: hospital Thrombotrak v practice near patient testing (NPT) results

		Practice		
		Out of range	*In range*	*Total*
Laboratory:	Out of range	72	32	104
	In range	18	74	92
	Total	90	106	196

Values are numbers of tests.

Table 2 Laboratory 1: hospital ACL v practice near patient testing (NPT) results

		Practice		
		Out of range	*In range*	*Total*
Laboratory:	Out of range	63	41	104
	In range	27	64	91
	Total	90	105	195

Values are numbers of tests.

Table 3 Laboratory 2: hospital KC-10 v practice near patient testing (NPT) results

		Practice		
		Out of range	*In range*	*Total*
Laboratory:	Out of range	38	42	80
	In range	29	32	61
	Total	67	74	141

Values are numbers of tests.

Table 4 Laboratory 3: hospital manual v practice near patient testing (NPT) results

		Practice		
		Out of range	*In range*	*Total*
Laboratory:	Out of range	22	27	49
	In range	9	10	19
	Total	31	37	68

Values are numbers of tests.

Table 5 Sensitivity and specificity of practice near patient testing (NPT) compared with hospital gold standard testing

Laboratory	*Sensitivity*	*Specificity*
Laboratory 1, TT	69%	80%
Laboratory 2, ACL	61%	70%
Laboratory 3, KC-10	48%	52%
Laboratory 4, manual	45%	53%

TT, Thrombotrak.

were 54% for laboratory 1, 52% for laboratory 2, and 54% for laboratory 3.

The correlation between INRs obtained on the practice Thrombotrak with those obtained on a Thombotrak in laboratory 1 showed a correlation coefficient (r) of 0.96, with r values for the practice derived results compared with laboratory 1 (ACL) of 0.89, laboratory 2 (KC-10; fig 1) of 0.86, and laboratory 3 (manual) of 0.92.

Tables 1–4 outline the numbers of tests whereby a clinically significant difference would have arisen depending on where the test was performed (that is, where practice and laboratory results are discrepant for in-range values). Sensitivity in this instance is defined as the proportion of results from the same sample being within the individual therapeutic range on both methods being compared; specificity is defined as the proportion of results being outside the therapeutic range using both methods. Thus for laboratory 1, Thrombotrak v practice, 50 of 196 tests (26%) would have resulted differing doses of warfarin being given. The figures for laboratory 1 ACL, laboratory 2, and laboratory 3 v practice results were: 68 of 195 (35%), 71 of 141 (50%), and 36 of 68 (53%), respectively. Taking the laboratory derived result as the gold standard, and analysing results as being in or out of range defined by clinical condition, according to British Society of Haematology guidelines,[14] the sensitivity and specificity of practice derived NPT INRs against the gold standards of the different laboratories are illustrated in table 5.

Although the correlation between the practice results and laboratory 1 Thrombotrak results is very good, there is a small positive bias of 0.28 on average in the practice results. The correlation between practice and laboratory 1 ACL shows that the practice INRs are consistently higher than the laboratory results, by 0.41 on average. There is a similar but greater discrepancy for laboratory 2 KC-10 (fig 1), where the mean bias was 0.56, and laboratory 3 manual, where the mean bias was 0.59. In all three cases bias tended to become greater as the INR increased. The predicted mean bias at an INR of 4.0 would be 0.48, 0.91, and 1.55, respectively.

Discussion

This study has highlighted the problems of varying INR results from the same blood sample. The implications of this are of great importance given the increasing pressure on primary care to undertake therapeutic monitoring of oral anticoagulation. We have shown that up to 50% of dosing decisions may be made differently according to the method of INR determination. This is a highly clinically significant finding since over and under dosing of warfarin can carry substantial risk.

The INR system was designed to overcome these differences and provide consistency in the measurement of the therapeutically induced coagulation defect, regardless of the method or site of testing. On these data, patients being monitored through two laboratories (2 and 3) would require larger warfarin doses to achieve therapeutic INRs than patients being monitored by either laboratory 1 or in primary care. One possible explanation for the variation in comparative INR measurements will be inadequate performance within the laboratory, to a level that falls below quality assurance programmes. All of the laboratories in this trial were subject to at least one external quality assurance programme (all were under NEQAS), but the results of their performance are not available to the authors since this is a confidential inquiry. However, clearly one possible explanation for the discrepancies in comparative INR measurements could have been that the performance in one or all of the clinics fell below the EQA standard.

Naturally, this does not negate the findings of this study (because it measures actual practice), but it may provide a further explanation for the variation in levels. This possibility reinforces the essential involvement of any centre

performing diagnostic testing, whether in primary or secondary care, to join an appropriate EQA scheme.

These primary care data reconfirm laboratory findings that the INR is influenced by the reagent used to measure it.[15-17] These data also show that the INR system does not adequately standardise for the different methods of testing, although the factors leading to this are probably multiple. The derivation of the ISI is currently performed against different WHO reference materials which may be one source of error. The differing thromboplastins used have varying sensitivities which are not fully accommodated by the INR.

This study is the first primary care based study of INR reliability. The results, particularly the correlation between results derived using the same technology, indicate that trained primary care nurses can perform the INR test as well as experienced laboratory staff. If primary care is to become more involved with therapeutic monitoring of oral anticoagulation, it is important that close links are forged between pathology laboratories and practices to ensure that differences in INR results obtained are kept to a minimum, with internal and external quality assurance procedures being organised through the local laboratory. In turn, hospital laboratories must adopt more consistent methods of INR estimation if their recommendations are to be reliable. The INR can be measured as consistently and safely in general practices as in hospital laboratories. The validity of derived INR results is as much a problem in hospital settings as in primary care and requires further investigation of the causes.

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